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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,610	07/25/2001	Shui-on Leung	018733-1053	3464

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 09/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,610	LEUNG, SHUI-ON	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *21-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-20, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that a search of claims 1-41 presents no undue burden on the Examiner (see page 2 of response). This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. In addition the Groups are distinct as indicated in the restriction requirement. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 21-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

3. Claims 1-20 are under examination.

Specification

4. The disclosure is objected to because of the following informalities

a) The first line of the specification needs to be updated to claim priority to the provisional application 60/220,782, filed 7/25/00.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 5, 7, 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 7, and 8 are indefinite for reciting the term "derivative" in claim 5. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the domains are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derivative" of the domain is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, fragments, chemically derivatized molecules, or even mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a

definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7, 9-12, 16-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10).

The claims recite a target binding protein comprising a first polypeptide comprising a scFv and an immunoglobulin-like domain and a second polypeptide of a scFv and an immunoglobulin-like domain wherein the scFv form two binding sites and the two immunoglobulin-like domains associate to form a third binding site. Further claimed is wherein the scfv and immunoglobulin-like domains are linked by a constant region associates with a disulfide bond and the domains are linked by a linker and wherein at least two of the three domain binding sites have different binding or the same specificity, and further the polypeptide comprises a peptide tag, a cytokine, wherein the target is a tumor antigen and surface protein of T cells.

Schoonjans et al teach scFv molecules conjugated through a CL or CH1 by a linker to a VH or VL and a second polypeptide comprising a scFv and a CL or CH1 and a VL or VH (see entire document, especially Figures 7A, 9A) and the molecules can bind two of the same antigens (Figure 9A) or different antigens (figure 7A) and the molecules have a disulfide bond in the extra amino acid sequence which is the constant region (see figures) and the molecules can have a tag or cytokine or other molecules attached to the binding sites (see page7).

9. Claims 1-2, 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al (WO 94/09131, published 4/94, IDS #10).

The claims recite a target binding protein comprising a first polypeptide comprising a scFv and an immunoglobulin-like domain and a second polypeptide of a scFv and an immunoglobulin-like domain wherein the scFv form two binding sites and the two immunoglobulin-like domains associate to form a third binding site wherein at least two of the three sites have different binding or the same specificity.

Harris et al teach a polypeptide comprising a scFv with a VL and a polypeptide with a scFv and a VH (see Figure 4) and the molecules can be trivalent and association domains of VL and VH and the scFv sites can be the same or different and the third site can be different from the two other sites (see page 26).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al (WO 99/37791, published 7/29/99, IDS #10) as applied to claims 1-7, 9-12, 16-19 above, and further in view of Leung et al (U.S. Patent 6,254,868, filed 11/98) and Lindhofer et al (U.S Publication US20002/0051780, filed 9/97).

Claims 1-7, 9-12, 16-19 have been described supra. Claims 8, 13-15 and 20 recite wherein the linker is SEQ ID NO:1 and SEQ ID NO:2 and wherein the first polypeptide or second polypeptide has a N-glycosylation site with a carbohydrate and a conjugate to the carbohydrate is a toxin and the molecules bind CD28 and CD3.

Schoonjans et al has been described supra. Schoonjans et la also teach the molecules bind CD3. Schoonjans et al does not teach a N-glycosylation site or a toxin linked to the carbohydrate site or that the molecules bind CD28 and CD3 or the linkers

of SEQ ID NO:1 and 2. These deficiencies are made up for in the teachings of Leung et al and Lindhofer et al.

Leung et al teach adding a carbohydrate recognition site in the antibody fragment and conjugation to toxins or labels for therapy (see entire document).

Lindhofer et al teach bispecific and trispecific antibodies wherein the molecule binds a tumor antigen and CD3 and CD28 (see page 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al because Leung et al teach engineered antibodies with added glycosylation sites and conjugation to toxins and other molecules for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al and bind the antigens of CD3 and CD28 as

taught by Lindhofer et al because Lindhofer et la teach trispecific molecules for targeting tumors and T cells and the molecules are directed to killing tumor cells (see page 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Schoonjans et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al and bind the antigens of CD3 and CD28 as taught by Lindhofer et al because Schoonjans et al teach trispecific molecules binding to CD3 and tumor antigens and conjugation of other molecules such as toxins and cytokines for treatment of diseases. It would have been obvious to label the molecules with the method of Leung because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to use the claimed linkers because any linker would satisfy the requirement of separating the domains.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claims 1-2, 9-10, 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris et al (WO 94/09131, published 4/94, IDS #10) as applied to claims 1-2 and 9-10 above, and further in view of Chaudhary et al PNAS 87:1066-70, 1990) and Leung et al (U.S. Patent 6,254,868, filed 11/98).

The claims have been described supra.

Harris et al has been described supra. Harris et al does not teach a conjugate at the C-terminal of the polypeptide or a glycosylation site for conjugation to toxins or

binding to toxin and tumor antigens. Theses deficiencies are made up for in the teachings of Chaudhary et la and Leung et al.

Chaudhary et al teach fusion protein at the C terminus to scFv for therapy.

Leung et al teach adding a carbohydrate recognition site in the antibody fragment and conjugation to toxins or labels for therapy (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al or add a polypeptide to the C-terminus as taught by Chaudhary et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al add a polypeptide to the C-terminus as taught by Chaudhary et al because Leung et al teach engineered antibodies with added glycosylation sites and conjugation to toxins and other molecules for therapeutic and the method does not alter antigen binding and the molecules are used for therapeutics. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al or add a polypeptide to the C-terminus as taught by Chaudhary et al because Chaudhary et al teach adding a toxin to the C-terminus for

therapeutic reasons to target tumor cells. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a molecule comprising three binding sites as taught by Harris et al and add a glycosylation site and conjugate a toxin to the site as taught by Leung et al or add a polypeptide to the C-terminus as taught by Chaudhary et al because Harris et al teach the molecules are used for therapeutics and can bind toxins or cells (see page 4). It would have been obvious to label the molecules with the method of Leung because of the advantages disclosed of not altering the antigen binding or specificity and it would have been obvious to produce a fusion protein as taught by Chaudhary et al for targeting to tumor cells.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be

reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER